Is it time to replace the Wada test and put awake craniotomy to sleep?

*†Andrew C. Papanicolaou, †‡Roozbeh Rezaie, †§Shalini Narayana, †¶Asim F. Choudhri, †¶James W. Wheless, **Eduardo M. Castillo, ††James E. Baumgartner, and §¶Frederick A. Boop

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SUMMARY

The question we address here is whether the invasive presurgical brain mapping approaches of direct cortical stimulation and of the Wada procedure can be replaced by noninvasive functional neuroimaging methods (functional magnetic resonance imaging [fMRI], magnetoencephalography [MEG], transcranial magnetic stimulation and [TMS]). First, we outline the reasons for contemplating such a replacement. Second, we present evidence to the effect that the efficacy of the invasive and noninvasive methods, while suboptimal, is comparable. Third, we discuss additional advantages of noninvasive presurgical brain mapping and conclude that there are no longer compelling reasons for opting for invasive mapping in many if not most cases provided that the non-invasive methods are available.

KEY WORDS: Awake craniotomy, Wada test, Functional magnetic resonance imaging, Magnetoencephalography, Transcranial magnetic stimulation, Cortical stimulation mapping.

The purpose of presurgical brain mapping is to facilitate surgical planning, prevent or reduce morbidity, and optimize the therapeutic effects of surgery. At present, brain mapping is limited to the identification of the language- and memory-dominant cerebral hemisphere, and the identification of the somatosensory, motor, and language-specific cortical regions. The former is accomplished through the Wada procedure, and the latter through cortical stimulation mapping (CSM). These procedures are considered the “gold standards”—a term implying that the evidence they furnish is more trustworthy than evidence from other methods.

The advent of noninvasive functional neuroimaging now raises the possibility of replacing these “gold standards,” provided it offers equally trustworthy results. It will be argued here that these methods, namely magnetoencephalography
(MEG), functional magnetic resonance imaging (fMRI), and transcranial magnetic stimulation (TMS) do provide equally trustworthy results, and that therefore they may replace the Wada test and CSM in many if not most cases.

The compatibility of the language lateralization results of the Wada and the fMRI procedure has been attested to in a number of studies reporting perfect concordance\(^1\) or high concordance (95\%).\(^2,3\)

Equally high is the reported compatibility between the results of the Wada and MEG with respect to language lateralization, ranging from 87% concordance in the study with largest sample\(^4\) to 100% agreement in the first subsample of patients of the same series,\(^5\) with the rest of the studies reporting uniformly high or perfect agreement.\(^6–8\) Fewer studies report comparisons of laterality estimates for memory between fMRI and Wada, with some reporting high,\(^9\) and others also low, concordance,\(^10\) raising the questions (discussed later) as to which method is to be trusted.

Furthermore, considerably high is the degree of concordance between CSM and MEG localization of language-specific cortical patches. In a study involving a small patient sample, Simos et al.\(^11\) showed compatibility of CSM and MEG for localizing receptive language-specific cortical sites, as did a second study by Castillo and colleagues\(^12\) involving 47 patients. Similarly, presurgical expressive language mapping with navigated TMS is highly successful, and the results correlate well with those of CSM (overall sensitivity of 90.2\%, specificity of 23.8\%, positive predictive value of 35.6\%, and negative predictive value of 83.9\%),\(^13,14\) as well as those of MEG.\(^14\) In addition, Taramore et al.\(^14\) demonstrated that the maps of the motor system generated with TMS correlate well with those generated by both MEG imaging and CSM. Equally high is the concordance of localization estimates of the motor and somatosensory cortex between intraoperative electroencephalography (EEG) and preoperative MEG estimates,\(^14,15\) as is that between invasive electrophysiology and TMS.\(^16\)

However, provided that the degree of concordance between invasive and noninvasive methods is not perfect (and sometimes low as in the case of memory lateralization mentioned earlier) the question becomes: The results of which of the two sets of methods is to be considered valid? On the basis of the assumption that CSM and the Wada are the “gold standards,” the tendency is to consider discordant estimates as failures of the neuroimaging methods. However, if that assumption is put to the empirical test it becomes obvious that the results of neither CSM nor Wada should be considered any more valid than the results of the noninvasive methods. For example, using CSM, Ojemann\(^17\) reported extensive temporal lobe involvement in receptive language tasks such as naming, yet Sanai et al.\(^18\) found a paucity of naming sites in the same region using CSM. In addition to limited reliability, CSM has limited predictive value with respect to postsurgical language and memory performance. For example, Ojemann and Dodrill\(^19\) reported 80% predictive accuracy of CSM in determining verbal memory performance postoperatively, and Cervenka et al.\(^20\) demonstrated that in 7 of 11 patients, postoperative language performance was not anticipated by the CSM mapping results. Moreover, Cervenka et al.\(^21\) also reported that three of four patients who underwent operation presented language deficits that were not predicted by CSM. In addition, Hermann et al.\(^22\) in their review of the results of eight centers involving 217 patients, concluded that neither intraoperative nor extraoperative CSM-guided surgeries are any more effective in reducing postsurgical naming deficits than non–CSM-guided surgeries are.

The efficacy of the Wada procedure is also lower than would be expected for a gold standard procedure for predicting the likelihood of postsurgical language and memory deficits. In contrast, comparisons show that fMRI has better predictive efficacy than the Wada test.\(^23,24\) Equally limited is the efficacy of the Wada procedure in predicting memory outcome. Indeed, prediction of verbal memory performance postoperatively varies from good\(^25\) to very low.\(^24,26\) Meanwhile, dozens of studies are conducted every year for the purpose of fine tuning the noninvasive methods in revealing with increasing reliability brain regions involved in different aspects of memory and language performance using fMRI,\(^27–28\) MEG,\(^29,30\) and lately TMS\(^13,14\) and verifying the validity of the findings, mainly against prior knowledge gained from lesion studies.

Therefore, given that the validity of the data of CSM and of the Wada is limited, there is no justification in considering them more trustworthy than data supplied by neuroimaging, in those few cases that the results are in fact discordant, especially in view of the report of Janecek et al.\(^31\) that fMRI predicts postsurgical naming performance better than the Wada (7 of 10 patients). Clearly, identifying limitations and shortcomings of the invasive procedures not shared by the noninvasive ones, by no means guarantee that the latter are limitation free. In fact, fMRI, positron emission tomography (PET), and MEG share two very serious limitations: First, not all the brain regions that appear activated, especially in tasks evaluating higher order functions like language and memory, are necessary for these functions. For example, whereas in nearly all speech production tasks there is substantial bilateral activation, the activation of the minor hemisphere is in all likelihood not necessary, since the patient can still perform the task during anesthetization of the minor hemisphere during the Wada and since expressive aphasia typically results from lesions of the dominant hemisphere. Therefore, the fact that language production correlates with activation of both hemispheres does not imply that areas in both hemispheres are causally related to the production of speech. Similarly, the presence of many activated areas within the dominant hemisphere does not guarantee that all of them are necessary for the task. Therefore the noninvasive methods may provide data of low specificity. A second basic and common limitation to the
noninvasive methods (MEG, PET, and fMRI) is related to the phenomenon of bilateral activation and consists in the determination of the appropriate ratio of the amount of activation that indicates actual lateralization of language or memory. This problem, however, has been largely solved in the context of prospective studies where the so-called laterality index (LI) has been established for both MEG\textsuperscript{13,32–35} and fMRI.\textsuperscript{24,36,37}

The practical question of course remains: Given that both types of methods are suboptimal, which type should be used preoperatively to address issues of lateralization and/or localization in any given case? We propose here that given the compatibility of the two sets of methods, both in terms of their concordance in most cases and their imperfections in few cases, the noninvasive methods should be used as a matter of course because, in case their results are ambiguous, testing can be repeated and the results of the different ones cross-validated (e.g. of fMRI or MEG against TMS for expressive language and motor mapping; MEG and fMRI for receptive language, and so on). And only if the ambiguity is still not resolved should CSM or the Wada be performed in the hope that they may resolve it.

Moreover, although both types of methods have limitations, the following ones, specific to the invasive but not to the noninvasive methods, render the latter preferable. First, the invasive procedures, namely the Wada, are associated with appreciable morbidity, ranging between 3 and 5\textsuperscript{\%}.\textsuperscript{38,39} Second, they are associated with patient discomfort often leading to discontinuation, particularly in the case CMS procedure. In contrast, no morbidity and only minor discomfort is associated with neuroimaging. Third, CMS cannot identify the memory-specific circuitry, which lies far from its reach, unless the limbic brain were to be probed with depth electrodes. Moreover, CMS cannot identify any eloquent cortex located under surface lesions. Equally uncertain may be the results of the Wada procedure for assessing memory because delivery of the sodium amobarbital to the hippocampal formation is not always possible\textsuperscript{40,41} and because the structure of the Wada protocol does not allow for separate estimation of hemispheric dominance for verbal and for nonverbal encoding, although there is evidence of stimulus-modality–specific encoding in the left and the right hippocampus.\textsuperscript{42,43} Needless to say, fMRI can discern the involvement of all brain structures associated with memory, both neocortical and paleocortical, and because it can be repeated, it can identify distinct components of the memory-specific brain circuitry.

A fourth and a fifth limitation of CSM and of the Wada are intimately related to the narrow time window in which these tests must be performed: Repetition of the procedure for establishing reliability of the results is nearly impossible in the case of Wada and very restricted in the case of CSM. Moreover, neither the CSM nor the Wada may probe for the mechanisms of a host of different cognitive operations that are subsumed under “language” and “memory.” Yet, the neuronal networks of such operations can be assessed separately in the context of several neuroimaging sessions. A sixth limitation specific to CSM is the inability to precisely control the spread of the current (see below) and the limitation specific to the Wada procedure is the inability to control for cross flow, rendering uncertain the degree of functional suppression of the hemisphere injected.\textsuperscript{41} A seventh problem, also reducible to the time constraints, is the inability to control for situational variables that may corrupt the integrity of the data. Attention lapses on the part of the patient in the crowded Wada suite where a number of tasks have to be done under time constraints may well produce misleading data, the integrity of which is impossible to ascertain because the procedure is done only once. In the case of CSM, situational variability is mostly contributed by the following factors: (1) anesthesia level, not always optimal for keeping the patient comfortable and at the same time sufficiently alert to complete the task; (2) current leakage along the cortical surface contingent on tissue hydration; and (3) timing of the delivery of CMS stimuli with respect to the task stimuli, which usually varies from trial to trial given that typically task-specific stimuli and the stimulating current are delivered manually and not automatically through a computer to control the timing of events. Once again, none of these limitations apply to noninvasive brain mapping methods. Eighth, neither CSM nor the Wada test can supply information about the primary visual and auditory cortex that both MEG and fMRI can readily supply. Finally, both CSM and the Wada test require alertness and cooperation on the part of the patient. Thus CSM and the Wada cannot be used with patients with attention deficit and hyperactivity problems, patients in a state of confusion, patients with encephalopathies, or patients who are very young. None of these limitations apply to neuroimaging, where localization of sensory, motor, and even receptive language cortex can be accomplished with the patient under sedation.\textsuperscript{44}

For all the preceding reasons we propose that it is time for the Wada and the CMS procedures to be replaced as the methods of choice in many if not most cases and for awake craniotomy to be put to sleep.

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